# Spicing it up - synthetic cannabinoid receptor agonists and psychosis - a systematic review

Melissa Hobbs

Nicola J Kalk

Paul D Morrison

James M Stone

**Abstract**

Synthetic cannabinoid receptor agonists (SCRAs) are suggested to have increased potential to induce psychosis compared to natural cannabis (NC). In this review we synthesise current knowledge about the association of SCRA use with psychotic symptoms. Following a literature search we identified 2 toxicology reports, 4 case-control studies, 3 cross-sectional studies and 15 case reports. In each of the case reports, we identified the presence or absence of symptoms based on the items of the Postitive and Negative Syndrome Scele (PANSS). The toxicology reports highlighted the main presenting features as being toxic psychosis and delirium (40%), agitation (10%) and hallucinations (4-7%). The median age was 25 years, and around 80% cases were male. Cross-sectional studies reported that SCRA use was present in approximately 10-13% patients presenting to acute psychiatric services, and was often the cause of their presentation, and that psychotic symptoms were present in 15% patients attending emergency departments following SCRA use. Case-control studies reported that SCRA use was significantly associated with psychotic symptoms and that SCRA users had higher levels of positive psychotic symptoms than NC users. The case reports supported the association of SCRA use with a wide range of positive and negative psychotic symptoms as well as with self-harm, agitation and aggressive behaviour. SCRA use is relatively prevalent in patients with psychosis and may lead to psychotic symptoms in individuals with no past psychiatric history. Further work is required to understand the long term risks of SCRA use and optimal management strategies.

Key words: Cannabis, Synthetic, SCRA, NPS, Psychosis, Schizophrenia,

**Introduction**

Since the mid 2000's, new psychoactive substances (NPS) have emerged as a global public health concern. NPS belong to diverse chemical groups and are comprised of substances of abuse intended to produce similar effects to existing drugs such as natural cannabis (NC), cocaine, heroin, lysergic acid diethylamide (LSD), 3,4-Methyl enedioxy methamphetamine (MDMA) and methamphetamine (UNODC, 2017). Of the 739 NPS reported to the United Nations Office on Drugs and Crime in 2016, synthetic cannabinoid receptor agonists (SCRA) constituted the largest known category, making up 32% of the total number (UNODC, 2017).

NPS use is rare in the United Kingdom, with an estimated 0.4% of the population having used them in the last year according to the most recent estimate (ONS, 2017). Two thirds of NPS users reported SCRA use. Despite being used by a relatively small proportion of the population, SCRA use is of concern because use is concentrated in vulnerable groups (Blackman and Bradley, 2017). There are, however, varying reports on SCRA consumer demographics including suggestions that those who abuse the drug are predominantly male, previous NC users, homeless or individuals who identify as LGBT (Barratt et al., 2013; Manseau et al., 2017; Miller and Stogner, 2014). There is also some evidence to suggest that the use of SCRAs is more common amongst the prison and homeless populations (Kalk et al., 2016). This growing problem is underscored by a recent finding of The Prisons and Probation Ombudsman that 19 fatalities over a two and a half year period were highly likely to have been proceeded by the use of NPS in UK prisons (HMIP, 2015).

Public health concerns related to SCRAs revolve around potency, with SCRAs having significantly higher binding affinity to CB1 and CB2 receptors compared to

tetrahydrocannabinol (Wiley et al., 2016). Associated with this is the concern that this higher potency may lead to higher risk of toxicity and the potential that use may lead to fatalities (UNODC, 2017). Additionally, there continues to be a lack of knowledge regarding the contents of substances marketed as synthetic cannabinoids, which can be variable in concentration and make-up (UNODC, 2017). Substances such as the synthetic opioid *O*-desmethyltramadol, caffeine and the β2-agonist clenbuterol have all been identified in SCRA products (Kersten and McLaughlin, 2015). SCRAs are most commonly found in 'herbal' mixtures composed of a liquid SCRA solution, which has been dissolved in a solvent and then sprayed onto plant material. However, this approach leads to areas of greater SCRA concentration (known as 'hot spots'), which can put users at risk of overdose (Dresen et al., 2010). Whilst the plant material is intended to be smoked, liquid SCRA solution may also be administered via vaporisation (UNODC, 2017). SCRAs are sometimes found in tablet form, as a white crystalline solid or powder intended for oral consumption or nasal insufflation (UNODC, 2017).

Several recent reviews are available on the adverse clinical effects of SCRAs (Gunderson et al., 2012; Tait et al., 2016). Such reviews document an increasing catalogue of adverse effects, which are wide ranging and include both physical and psychological manifestations. Briefly, SCRA intoxication is dominated by neuropsychiatric, cardiovascular, and abdominal signs, with agitation, paranoia, tachycardia, hypertension, abdominal pain and vomiting being among the most common (Castaneto et al., 2014; Muller et al., 2017; Vearrier and Osterhoudt, 2010).

The association between NC use and psychosis has been well documented (Fergusson et al., 2006). SCRAs are hypothesised to have an increased potential to induce psychosis compared to NC, because they have a higher affinity for the CB1 receptor and act as full agonists (Murray et al., 2016). In this review we aim to synthesise current knowledge about the association of SCRA consumption with psychotic symptoms – including toxicology data, epidemiological studies, case-control studies and case reports.

**Experimental Procedures**

In November 2017, English language studies were identified from Ovid MEDLINE (PubMed), PsychINFO, PsychArticles, Embase and Google Scholar databases for observational studies and case reports related to SCRA use and psychotic symptoms. Search terms included (Synthetic Cannabinoid OR Synthetic Marijuana OR Synthetic Cannabis OR Legal High OR Spice OR K2) AND (Psychosis OR Schizophrenia). Article reference lists were examined for other relevant papers to be included. Only peer-reviewed publications that involved SCRA use in humans were considered. Systematic reviews were excluded from abstraction but were hand-searched as a source of additional material. Case reports were excluded if psychotic symptoms were not directly observed by a medical professional and a diagnosis of psychosis was not clearly documented. Multiple case reports were also excluded where the number of patients within a group presenting with psychosis was unclear. Case reports where patients were undergoing a psychotic episode prior to SCRA use were also excluded. The target substance was any SCRA, including self-reported and analytically confirmed cases. We included case reports where SCRAs were the only reported substance use, or in the case of poly-substance use, where the authors of the case report stated that SCRAs were the primary substance involved.

**Study Selection**

After removal of duplicates, 303 papers were identified and abstracts screened. Of these, 87 were excluded as they did not report psychotic symptoms or SCRA use. The full text of remaining 216 papers was searched, and a further 192 papers excluded due to not fulfilling the inclusion criteria (Fig 1). After abstraction and full text screening, a total of 24 articles were selected for review: 2 toxicology reports (Monte et al., 2017; Waugh et al., 2016), 4 case-control studies (Altintas et al., 2016; Bassir Nia et al., 2016; Shalit et al., 2016; Welter et al., 2017), 3 cross-sectional analyses (Glue et al., 2013; Manseau et al., 2017; Vallersnes et al., 2016) and 15 case reports (Barcelo et al., 2017; Benford and Caplan, 2011; Coppola and Mondola, 2017; Hurst et al., 2011; Johnson et al., 2011; Mahgoub and Young, 2017; Meijer et al., 2014; Muller et al., 2017; Oliveira et al., 2017; Oluwabusi et al., 2012; Ozer et al., 2016; Roberto et al., 2016; Rojek et al., 2017; Samaan et al., 2016; Van der Veer and Friday, 2011) (Figure 1).

In order to summarise the symptoms described in the case reports, we used the Positive and Negative Syndrome Scale (PANSS) items (Kay et al., 1987) as a structure for systematically analysing the reports. For each item on the PANSS we determined whether related symptoms or behaviours were mentioned in the report (i.e. hallucinations, delusions, hostility). If the report mentioned a symptom related to a particular PANSS item, then we recorded that item as being present, otherwise it was recorded as absent. Thus for a particular case report, a score of 1 or 0 could be recorded for each PANSS item.. In addition, the mention of drug-related suicidal ideation, self-harm, insomnia or amnesia, and any past psychiatric history in each report was recorded.

## Results

### *Toxicology Reviews*

Of the nearly 40,000 cases reported to the registry of the national Toxicology Investigators Consortium (ToxIC) in the USA between 2010 and 2015, 353 cases were ascribed to SCRA toxicity (Monte, A.A., et al, 2017). Overall SCRA toxicity cases reported to ToxIC follow an upward trend, with only 6 reported in 2010 compared to 112 reported in 2015, suggesting a growing problem (Monte et al., 2017). In the UK a similar upward trend was observed in the 510 enquiries related to SCRA exposure dealt with by the National Poisons Information Service (NPIS) between 2007 and 2014 (Waugh et al., 2016). Clinical presentation varied with the most common s recorded by the ToxIC Registry being agitation in the setting of toxic psychosis and delirium, which was seen in 146 (41.4%) patients (Monte et al., 2017). In contrast agitation and aggression were only reported in 10.4% of cases reported to the NPIS 2014 (Waugh et al., 2016). In both the UK and USA hallucinations were less commonly reported than agitation, seen in 7.1% of patients in the ToxIC registry and 4.6% of those reported to the NPIS (Monte et al., 2017; Waugh et al., 2016). A median age of 25 was recorded by both the NPIS and ToxIC registry in regards to SCRA users, with around 80% of cases listed as male by both databases (Monte et al., 2017; Waugh et al., 2016). 37% of cases received treatment with benzodiazepines, 10% were prescribed antipsychotics and 9% received both (Monte et al., 2017). However administration of either class of drugs did not seem to reduce the probability of intensive care unit (ICU) admission (Monte et al., 2017). The majority of cases reported to ToxIC were seen in the Emergency Department at first consultation, with 24% requiring ICU admission and one case resulting in death (Monte et al., 2017).

***Cross-sectional analyses***

Manseau and colleagues investigated the demographics of patients attending psychiatric emergency services in an urban setting in the USA who had reported SCRA use (Manseau et al., 2017). They found that approximately 11% of the patient records that they assessed had reports of SCRA use. SCRA users were primarily non-white (90%), male (96%), with a history of contact with the police (35%) and homeless (85%). They also often had pre-existing psychotic symptoms (70%), a history of a diagnosis of a psychotic disorder (40%), previous hospital admission (71%), comorbid substance use (63%), agitation (23%) and the need for extended psychiatric observation (16%) and admission (35%).

Glue and colleagues reported SCRA-related admissions to an acute psychiatric ward in New Zealand between January and April 2014 (Glue et al., 2013). They reported that 13% of all admissions to the ward during this period (17 patients with 21 admissions) were related to K2 use. For 4 of the patients this was a first admission, and for the remaining 13, a further 4 presented for the first time with psychotic symptoms. Presenting features included psychotic and affective symptoms, as well as suicidal thoughts and behaviour. The mean duration of admission was 9 days, although in those with psychotic symptoms it was 13 days.

Vallersnes and colleagues reported data from the European Drug Emergencies Network between October 2013 and September 2014 on patients presenting to European emergency departments with acute drug toxicity (Vallersnes et al., 2016). They reported that 6.3% of attendances included psychotic symptoms. The median age was 29, 79% were male and 32% were admitted to a psychiatric ward. More than one drug was taken in 54% of cases. Psychosis

was present in 15% of patients who reported taking SCRAs. This compared to 57% on tryptamines, 23% on methylphenidate, 21% on LSD, 19% on psilocybe mushrooms, 14% on amphetamine and 10% on NC.

***Case-control studies***

Bassir and colleagues examined the records of 594 patients who had been admitted to a dual diagnosis psychiatric ward in the USA in 1 year (Bassir Nia et al., 2016). They studied the level of psychiatric symptoms in patients who had a history of SCRA use or NC use either singly or in combination. They found that those who used SCRA had significantly higher levels of psychotic symptoms than those who took SCRA and NC together, who in turn had higher levels of psychotic symptoms than those who took NC alone. SCRA users had the highest level of agitation, and users who took both SCRA and NC had the highest levels of aggression. SCRA users were also prescribed higher doses of antipsychotic medication.

Shalit and colleagues studied patients admitted to a psychiatric ward in Israel who reported SCRA use and compared them to patients admitted who reported NC but not SCRA use (Shalit et al., 2016). The SCRA users were younger than NC users, had longer admissions, and more marked psychotic symptoms (PANSS total score of 82.5 vs. 70).

Welter and colleagues reported the prevalence of SCRA use in a psychiatric inpatient population in Germany and compared those with a history of NC use to those with a history of SCRA use (Welter et al., 2017). They reported that 7% of all psychiatric inpatients under the age of 65 had a history of SCRA use (10% of those presenting with psychosis), whereas 43% of patients had a history of NC use. SCRA users tended to be younger than NC users (mean

age 26 vs. 32), male (71% vs 62%), be on a closed ward (81% vs 42%) and be psychotic on admission (71% vs 62%). Analysis of individual symptoms, based on a subset of the PANSS scale, reported during acute intoxication showed that NC users had more predominant negative symptoms whereas SCRA users had more marked positive symptoms, but the reported symptom profiles of the two classes of drug overlapped considerably.

Altintas and colleagues identified 50 patients who had been admitted to a psychiatric ward in Turkey following SCRA-induced psychosis (Altintas et al., 2016). They also identified 31 concurrently hospitalised patients with schizophrenia. The mean age of the SCRA patients was 29, whereas it was 43 in those with schizophrenia. The average age of first SCRA use was 23. Patients with SCRA-induced psychosis had lower PANSS negative scores (18 vs. 22.3), and higher HAM-A scores (17.8 vs 11.4). Both groups had similar levels of symptoms on PANSS positive scores and Brief Psychiatric Rating Scale (BPRS).

**Case Reports**

The case reports were 100% male, with a total of 30 cases. Five of these had a past psychiatric history (schizophrenia, bipolar affective disorder, post-traumatic stress disorder, cannabis-induced psychosis and amphetamine-induced psychosis) (Table 1 and 2). Not all case reports gave an age for each individual, but reported ages ranged from 16-66, with most cases being in their late teens or early twenties. The largest proportion of case reports were from the USA (22 cases), with the remaining 7 cases from Europe and 1 from Turkey. Case reports were divided into those that related to patients with a previous psychiatric history (PPH) and those with no previous psychiatric history (NPPH). Cases with a past psychiatric history tended to be slightly older than those without. There were a large variety of symptoms reported

spanning both positive and negative symptom domains. There was generally no clear distinction in the range and type of symptoms reported in people with or without a previous psychiatric history, although reports of blunted affect were more common in patients without any past psychiatric history (Table 3).

There were incidents of self-harm across both groups including substantial burns related to one NPPH patient's paranoid delusions that his own hands were going to harm him (Meijer et al., 2014), and one patient who inflicted a penetrating wound to his neck requiring otorhinolaryngological surgery in the PPH group (Oliveira et al., 2017). Violent behaviour was noted in one NPPH case report resulting in the death of a female relative (Rojek et al., 2017), which is consistent with previous reports of homicidal ideation in SCRA users (Glue et al., 2013).

Treatment was generally with second generation antipsychotic drugs, and symptoms resolved in most cases within 2 weeks, although relapse occurred in 4 cases where patients restarted SCRA or heavy NC use. In two cases where haloperidol was used, the psychotic symptoms did not completely resolve within 2 weeks.

**Discussion**

In this review, we found evidence for the association of SCRA use with psychotic symptoms, even in individuals with no past psychiatric history. It is remarkable that the range of symptoms reported overlapped very closely with schizophrenia, although one study in which symptoms were compared directly revealed that the symptoms were less severe in the SCRA group (Altintas et al., 2016). Interestingly, one case series reported that the psychotic

symptoms induced by SCRA in patients with schizophrenia were distinct from their existing psychotic symptoms (Celofiga et al., 2014).

We found evidence of hostility in 12.3% of cases with NPPH and 40% of cases with PPH. This is in keeping with previous reports of hostility associated with SCRA use (Monte et al., 2017; Waugh et al., 2016) and reflects reports of increased levels of violence associated with NPS (Shafi et al., 2017). A more recent study of 5 specific SCRA compounds reported aggression and agitation in over 80% of patients presenting with intoxication from these substances to emergency departments (Hill et al., 2018).

SCRAs were originally developed to mimic the activity of delta-9-tetrahydrocannabinol ($\Delta^9$-THC) (the major psychoactive component of NC), which is a partial agonist of cannabinoid receptors CB1 and CB2 (Vardakou et al., 2010). $\Delta^9$-THC is thought to account for the association between NC and psychosis, whereas cannabidiol is thought to counteract this psychotic effect (Hervas, 2017). The findings of Bassir Nia and colleagues that isolated SCRA use is associated with psychosis to a greater degree than SCRA and concurrent NC use (or NC use alone), may be due to cannabidiol exerting an antipsychotic effect when consumed alongside SCRAs, although the relatively low concentration of cannabidiol in modern NC makes this less likely (Bassir Nia et al., 2016). Alternatively, the increased psychotogenicity of SCRAs may be due to them being high affinity full agonists at CB1 receptors whereas $\Delta^9$-THC is a partial agonist (Hess et al., 2016; Seely et al., 2012). Indeed, SCRAs can have a potency several hundred fold greater than $\Delta^9$-THC (Guhring et al., 2001). Furthermore, it appears that modifications to existing SCRAs are being made further increase the affinity for the CB1

receptor (Gamage et al., 2018), with novel SCRAs showing the highest potency at the CB1 receptor becoming more commonly available on the market (Marusich et al., 2018).

Due to stronger action at the CB1 receptor, SCRAs are thought to more strongly inhibit GABA mediated neurotransmission than $\Delta^9$-THC (van Amsterdam et al., 2015). This in turn is thought to lead to overactivation of dopaminergic activity in the prefrontal cortex, resulting in psychotic symptoms (Bossong and Niesink, 2010). Additionally, a recent MRI study suggests that long term use of SCRAs is associated with abnormal white matter integrity, which has also been proposed as a theory for the mechanism of vulnerability to psychosis (Zorlu et al., 2016).

The similarity of positive and negative symptom severity in those experiencing psychosis associated with schizophrenia and substance induced psychotic disorder has previously been described (Srisurapanont et al., 2011). Indeed, several drug models of schizophrenia have been proposed, including $\Delta^9$-THC (Carhart-Harris et al., 2013; Steeds et al., 2015). In support of this theory, certain alterations in neurophysiological measures occurring in NC administration, also take place in patients with schizophrenia (including mismatch negativity, P50 suppression and P300 potential) (Gallinat et al., 2012). Likewise cannabidiol has proved efficacious against psychotic symptoms in schizophrenia, suggesting that these symptoms may be linked to activation of cannabinoid receptors (Leweke et al., 2012).

It is perhaps unsurprising that a young mean age was noted in patients with psychosis who are SCRA users, considering that SCRA products tend to be marketed to attract a young

demographic (Vardakou et al., 2010). Internationally, peak use appears to occur in the late teens and early twenties (Loeffler et al., 2016).

Where stated, medical therapy described in the case reports ranged from antipsychotics (haloperidol, risperidone, olanzapine, quetiapine, aripiprazole and amisulpride), to benzodiazepines (clonazepam and lorazepam) and mood stabilisers (divalproex). Antipsychotic medications exert their effects by antagonising dopamine (D2) receptors (Kapur and Mamo, 2003). Neuroscientific studies have identified atypical dopamine activity in NC users, which therefore could underlie its association with psychosis in SCRA users (Fergusson et al., 2006). Although there are no specific antidotes or treatments for SCRA toxicity, it has been suggested that the CB1 receptor antagonist rimonabant (a former treatment for obesity) could be an option for the medical management of SCRA overdose (Ford et al., 2017). However, due to psychiatric disturbances, rimonabant, was withdrawn by the European Medicines Agency in 2008 and clinical research into potential uses has since been suspended.

A major factor in the evolution of SCRAs appears to be a bid to evade the increasing global regulation of SCRA production, possession and supply. When first sold, the SCRA Spice, which is commonly referred to in the literature and case reports detailed here, was thought to consist of JWH-018 and JWH-073 (Seely et al., 2012). Formerly known as ‘legal highs’, the law is slowly catching up with NPSs. Following the Psychoactive Substances Act (PSA) of 26 May 2016, the production and supply of NPS became illegal within the UK (PHE, 2017). With regard to the efficacy of PSA as a deterrent to those selling such drugs, one study found that the online availability of the SCRA known as 'MDMB-CHMICA' fell from 47 to 38 websites between March and June 2016 (Haden et al., 2017). It is possible that SCRA toxicity will undergo a

decline in the UK following this change in the legislature, although clinical urine screening for SCRAs remains a challenge, which is likely to drive continued use in prison. The National Poisons Information Service Report (NPIS) for 2016/2017 noted a 73.2% reduction in telephone enquiries related to NPS and a 52.8% reduction in telephone enquiries related to SCRAs specifically (PHE, 2017). Additionally, accesses to the TOXBASE database related to SCRAs and NPS fell 33.5% and 63.8% respectively. It is however too early to tell if there is a causal link between the introduction of the PSA and this fall. It is also very possible that the fall itself is due to a drop in self reporting SCRA use to clinicians due a fear of repercussions relating to their illegality.

A more recent development involves modifications being made to the first generation 'parent' compounds detailed above. This has resulted in the evolution of three distinct generations of SCRAs, with second generation SCRAs including alkyl derivatives, N-methylpiperidines and benzoylindoles. Third generation SCRAs can be broadly classified into molecules where the indole ring has been replaced with an indazole or benzimidazole group, where the carbonyl group has been replaced with carboxylic or carboxy-amide functional group and quinolones with secondary cyclic structures and new nitrogen groups (Pintori et al., 2017). Despite these differences in structure, all SCRAs remain lipid soluble, non-polar and highly volatised with a high affinity for CB1 and CB2 receptors (Gamage et al., 2018; Marusich et al., 2018; Schoeder et al., 2018; Seely et al., 2012).

It is important to address the limitations of this review. Namely, there are many shortcomings when working with case report data. These include the degree of interpretation required when eliciting specific symptoms from descriptive and subjective case reports. The method

of comparing positive and negative symptoms was vulnerable to under-reporting of negative symptoms, and it is possible that patients were more likely to be selected for case reports if experiencing positive symptoms. Most of the case reports and studies examined for this review relied on the use of SCRAs being self-reported by the patient. Previously, a higher rate of psychotic disorders has been identified in studies where the presence of the SCRA was analytically confirmed, compared to self-report alone (van Amsterdam et al., 2015) and a recent emergency services case series found that only half of patients who had taken SCRAs reported doing so (Abouchedid et al., 2017). It is therefore possible that the cases that went unreported, and therefore were not written up or included in the data, may have provided conflicting information to the ones detailed here.

Associated with the problems of self-report is the fact that it is not possible to ascertain which particular chemical was taken on each occasion. There is considerable chemical diversity to synthetic cannabinoids, with new compounds being developed on an ongoing basis and it is not clear how differences in chemical structure might affect the pharmacodynamics profiles of these compounds (Fattore and Fratta, 2011). Certain SCRAs may be more available in particular areas or countries and so it is not clear how generalizable findings may be (Gol and Cok, 2017).

Relatively few studies were found that reported the demographics of psychotic SCRA users. Although they reported a similar mean age, small sample sizes dictate that further research is needed to confirm that a young demographic is associated with SCRA induced psychosis. Despite the lack of evidence however, it may be prudent for the clinician confronted with a psychotic patient in their twenties with a negative drug screen to consider the possibility of

SCRA involvement, particularly if there is pronounced agitation in combination with increased heart and blood pressure, and vomiting.

**Conclusion**

Early evidence suggests that SCRAs are associated with psychosis in a young demographic. Recent studies also suggest that there is a greater association between SCRAs and psychosis than NC and psychosis. Whether SCRA induced psychosis is a growing problem, or changes in the law are leading to a decline in SCRA use is unclear. Case reports examined here suggest that SCRA users with a previous psychiatric history may present with more positive symptoms compared to those with first episode psychosis. However, reliance on case report data is a limitation of this review and further case control studies are required to confirm this finding. Furthermore, clear treatment guidelines are required for clinicians giving medical care to individuals with suspected SCRA induced psychosis.

Figure 1: Prisma flow diagram of selection of papers.

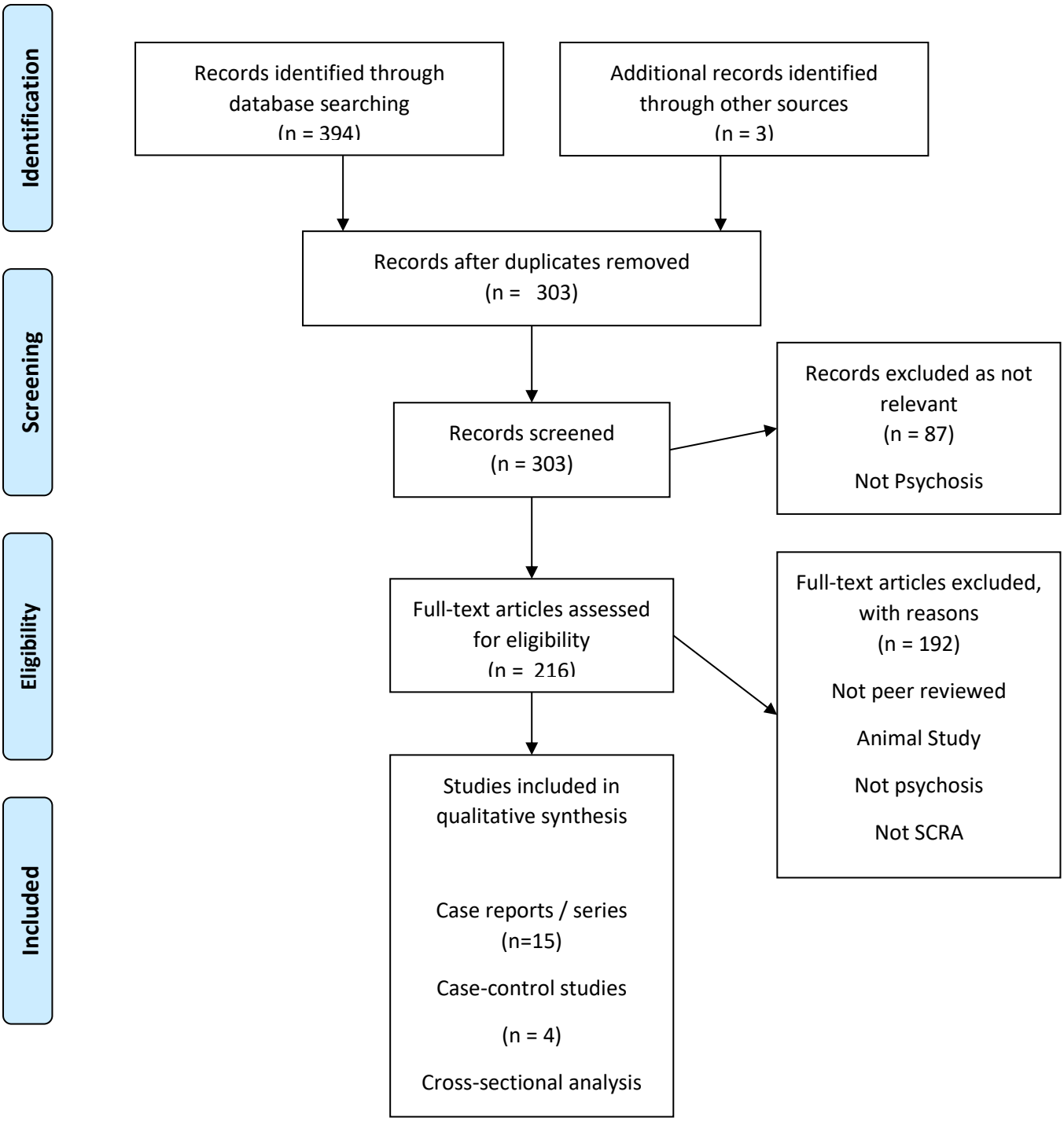

Table 1: First episode psychosis: Case reports of psychosis induced by SCRA use in patients with no previous history of psychosis

| **Study** | **Case(s), n: sex, age** | **Country** | **SCRA Brand Name / Compound / Analysis / Duration / Evidence of polysubstance abuse** | **Positive Symptoms** | **Negative Symptoms** | **General Psycho-pathology** | **Physical Signs & Symptoms** | **Other Symptoms** | **Treatment / Duration / Length of Stay** |
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| *Coppola, M. et al, 2017* | 1, male, 18, | Italy | JWH-122 / Gas chromatography mass spectrometry<br><br>Cannabis (History of heavy daily use).<br><br>Hallucinogenic mushrooms (once). | Visual hallucination (coloured geometric forms and animals)<br><br>**PANNS Positive symptom score** 8 | Blunted affect<br><br>**PANNS Negative symptom score** 8 | Anxiety<br><br>Tension<br><br>**PANSS General Psycho-pathology Score** 18 | Tachycardia | | 6 mgs daily of clonazepam<br><br>Symptoms re-occurred for 3 years during heavy cannabis use or periods of boredom<br><br>Monitored regularly for a year<br><br>**Overall** PANSS score of 34 |
| *Rojek, S., et al, 2017* | 1, male, 18 | Poland | Mr Green – No bad trip / AM-2201 / Gas chromatography mass spectrometry<br><br>Cannabis.<br><br>Legal Highs. | Delusions (of possession / being part of a film)<br><br>Hostility | Lack of spontaneity and flow of conversation | Anxiety<br><br>Motor retardation<br><br>Poor impulse control | Dyslalia<br><br>Sialorrhea<br><br>Wide pupils, unresponsive to light | Violent behaviour - murder of a female relative and attempted murder of two other victims by stabbing | Not stated |

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| | | | Immature personality disorder | | | | | | |
| *Mahgoub, N. and Young, R.C., 2017* | 1, male, 66, | USA | K2 / Self reported daily use for 2 months to self treat back pain<br><br>Cannabis (use in adolescence) | Delusions (Persecutory) | | | Tachycardia<br><br>Hypertension | | Risperidone (2 mg/d) - tapered and discontinued after 2 weeks |
| *Ozer, U., et al, 2016* | 1, male, 17, | Turkey | Bonzai / Self reported use most days for 10 days<br><br>Previous volatile substance abuse. | Delusions (paranoid, persecutory - Capgras syndrome delusions that his parents had been replaced)<br><br>Auditory hallucinations<br><br>Suspiciousness / Persecution | Lack of spontaneity and flow of conversation | Anxiety<br><br>Tension | Reduced appetite | Self-harm<br><br>Insomnia | Olanzapine 10mg/day – complete recovery achieved after 2 weeks. |
| *Meijer, K.A., et al, 2014* | 1, male, 26 | USA | Black Diamond / Self reported<br><br>Attention deficit disorder, treated with lis-dexamfetamine dimesylate and | Delusions (Paranoid - that his hands were going to harm him, resulting in an attempt to burn them off | | | | Self-harm (fourth-degree burns to the bilateral hands and forearms with | Burn resuscitation, multiple debridements, transradial amputation, toe transfer, myoelectric prosthesis |

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| | | | stable for a period of years | and “get the devil out.”) | | | | second-degree burns to the face) | |
| *Samaan, J., et al, 2016* | 1, male, 18 | USA | Self report 3-4 day use of an SCRA (and abstinence from cannabis for 1 month supported by a urine screen)<br><br>Cannabis | Delusions (Paranoid)<br><br>Auditory hallucinations | | Anxiety<br><br>Tension<br><br>Poor impulse control | Shortness of breath<br><br>Diaphoresis | Suicidal Ideation | Antipsychotic regimen<br><br>Symptoms subsided 2-3 weeks after discharge |
| *Roberto, A.J., et al, 2016* | 1, male, 18 | USA | K2 and Spice / Self reported<br><br>Cannabis (until the previous 3-4 weeks) | Delusions (Paranoid - thought insertion and broadcasting)<br><br>Conceptual Disorganisation<br><br>Auditory hallucinations (paranoid)<br><br>Excitement<br><br>Suspiciousness / Persecution<br><br>Hostility | Blunted affect<br><br>Emotional Withdrawal<br><br>Poor Rapport<br><br>Passive/ Apathetic Social Withdrawal<br><br>Lack of Spontaneity and Flow of Conversation | Mannerisms and Posturing<br><br>Motor retardation | | Insomnia | Lorazepam 2 mg orally PRN<br><br>Oral risperidone, 2 mg in the morning and 3 mg at night<br><br>Two week hospitalisation.<br><br>Relapse 2 weeks after discharge coinciding with SCRA use and medicinal noncompliance |
| *Oluwabusi,* | 1, male, 16 | USA | K2 / Self reported as | Delusions (Paranoid) | Passive/ Apathetic | Anxiety | | Insomnia | Quetiapine as an inpatient, changed to |

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| *O.O., et al, 2012* | | | significant and frequent Cannabis (suspected) | Conceptual Disorganisation<br><br>Visual hallucinations, Auditory hallucinations (musical)<br><br>Grandiosity<br><br>Excitement<br><br>Hostility | Social Withdrawal | Depression | | | aripiprazole secondary to dystonic reaction.<br><br>Relapse coinciding with SCRA use after 3 months.<br><br>Oral dispersible olanzapine 5mg (titrated to 15mg). |
| *Oluwabusi, O.O., et al, 2012* | 1, male, 17 | USA | K2 / Self reported for 1 month | Delusions (thought broadcasting)<br><br>Conceptual Disorganisation | Passive/ Apathetic Social Withdrawal | Somatic concern<br><br>Anxiety | | Insomnia | Olanzapine 15mg at night.<br><br>Relapse coinciding with SCRA use and medicinal noncompliance |
| *Hurst, D., et al, 2011* | 10, male, 21-25 | USA | SCRA only (2) / Self-reported (3 weeks to 1.5 years) (10)<br><br>Cannabis (8) | Delusions (Paranoid) (9)<br><br>Conceptual Disorganisation (4)<br><br>Visual hallucinations (2) | Blunted affect (6)<br><br>Lack of Spontaneity and Flow of Conversation (3) | Anxiety (2)<br><br>Motor retardation (6) | | Suicidal ideation (4)<br><br>Insomnia (6) | Hospitalisations between 6-10 days<br><br>Psychotic symptoms resolved (5 days – 5 months) |

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|---|---|---|---|---|---|---|---|---|---|
| | | | | Auditory hallucinations (4)<br><br>Disorganised behaviour (7) and speech (6) | | | | | |
| *Benford, D.M., et al, 2011* | 1, male, 20 | USA | Spice / Self reported | Visual hallucinations<br><br>Auditory hallucinations<br><br>Suspiciousness / Persecution | Poor Rapport<br><br>Lack of Spontaneity and Flow of Conversation | Anxiety | Tachycardia<br><br>Diaphoretic | | |
| *Johnson, L.A., et al, 2011* | 1, male, 23 | USA | Spice / Self reported / 96 hours and 48 hours before presentation<br><br>Cannabis (3 years earlier) | Delusions (Paranoid, persecutory – of being video taped)<br><br>Conceptual Disorganisation<br><br>Suspiciousness / Persecution<br><br>Disorganised behaviour | | Guilt | | | Symptoms spontaneously resolve 24 hours after presentation |
| *Van Der Veer N & Friday J., 2011* | 1, male, 20-30 | USA | Spice / Self reported 3-4 week history of smoking a 'bowl' of spice daily | Delusions (Capgras)<br><br>Conceptual Disorganisation | Stereotyped Thinking | Inappropriate affect<br><br>Poor attention | | Suicidal Ideation | Haloperidol<br><br>2 week hospitalisation (symptoms did not resolve completely) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Cannabis (stopped at time of Spice initiation) | | | | | | |
| *Barceló, B., et al, 2017* | 3, male 17 | Spain | Spice / Self reported | Delusions (Of possession and super powers) (3)<br><br>Grandiosity (3) | | Anxiety (3)<br><br>Tension (3)<br><br>Disorientation (3) | Tachycardia (3)<br><br>Mydriasis (1) | Temporary Amnesia (3)<br><br>Loss of Consciousness (3) | No medical treatment required |

Table 2: Case Reports of psychosis induced by SCRA use in patients with previous history of psychosis

| Study | Case(s), n: sex, age | Country | Psychiatric History / SCRA Brand Name / Compound / Analysis / Duration / Polysubstance abuse | Positive Symptoms | Negative Symptoms | General Psychopathology Symptoms | Physical Signs & Symptoms | Other Symptoms | Treatment / Length of Stay |
|---|---|---|---|---|---|---|---|---|---|
| *dos Santos Oliveira, P.M., et al, 2017* | 1, male, 32 | Portugal | Paranoid schizophrenia / Diagnosed 9 years earlier / Stable for a long period<br><br>Shiva Ultrastrong / Self-reported | Delusions<br><br>Excitement<br><br>Suspiciousness / Persecution | | Anxiety (extreme, vegetative) | Tachycardia<br><br>Mild hypotension | Suicidal Ideation<br><br>Self harm (penetrating wound to the neck) | Continuation of usual antipsychotic regime (monthly IM haloperidol decanoate 100mg, clozapine 200mg/day, lorazepam increased from 2.5mg OD to 2.5mg x3/day) / ENT surgery inpatient 2 weeks, psychiatric inpatient 2 weeks - |
| *Mahgoub, N. and* | 1, male, 65, | USA | Bipolar disorder / history of multiple | Delusions<br><br>Grandiosity | | | | Manic signs and symptoms | Risperidone (6 mg/d) and divalproex |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *Young, R.C., 2017* | | | psychiatric admissions<br><br>K2 / Self reported user for previous year<br><br>Alcohol and cocaine | | | | | (elated mood, pressured speech, increased energy level, decreased need for sleep) | (2000 mg/d); his serum valproate level was 91 µg/mL after 10 days on medication |
| *Müller, H., et al, 2010* | 1, male, 25 | Germany | Cannabis induced recurrent psychotic episodes<br><br>Spice / Self-reported 3g on 3 occasions<br><br>Cannabis | Delusions (of manipulation via an implanted chip in his abdomen)<br><br>Visual Hallucinations (Paranoid)<br><br>Auditory hallucinations (imperative voices) | | Anxiety | | | Amisulpride (800mg/d) for 2 years |
| *Van Der Veer N & Friday J., 2011* | 1, male, 20-30 | USA | Post-Traumatic Stress Disorder<br><br>Spice / Self reported 3-4 week history<br><br>Cannabis (stopped at time of Spice initiation) | Delusions (Paranoid - that his phone had been bugged and there were bullet holes in his house)<br><br>Conceptual Disorganisation<br><br>Suspiciousness / Persecution | Stereotyped Thinking | Inappropriate affect<br><br>Poor attention | | Suicidal Ideation | Risperidone<br><br>2 week hospitalisation (symptoms did not resolve completely) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Hostility | | | | | |
| *Van Der Veer N & Friday J., 2011* | 1, male, 20-30 | USA | Amphetamine induced prior psychotic episodes<br><br>Spike 99 / NOK reported him as regular user<br><br>Amphetamine | Delusions (Paranoid, persecutory – that he was from hell)<br><br>Conceptual Disorganisation<br><br>Suspiciousness / Persecution<br><br>Hostility | Stereotyped Thinking | Inappropriate affect<br><br>Poor attention | | | Haloperidol<br><br>2 week hospitalisation (symptoms did not resolve completely) |

Table 3: Percentage of individuals with no previous psychiatric history (NPPH) and those with previous psychiatric history (PPH) who experienced specific positive, negative and general psychopathology symptoms.

| **Positive Symptoms** | **NPPH % (n)** | **PPH % (n)** | **General Psychopathology Symptoms** | **NPPH % (n)** | **PPH % (n)** |
|---|---|---|---|---|---|
| Delusions | 88.0% (22) | 100.0% (5) | Somatic Concern | 4.0% (1) | (0) |
| Conceptual Disorganisation | 36.0% (9) | 40.0% (2) | Anxiety | 48.0% (12) | 40.0% (2) |
| Hallucinations | | | Guilt Feelings | 4.0% (1) | (0) |
| - *Auditory* | 36.0% (9) | 20.0% (1) | Tension | 24.0% (6) | (0) |
| - *Visual* | 20.0% (5) | 20.0% (1) | Mannerisms and Posturing | 4.0% (1) | (0) |
| Excitement | 8.0% (2) | 20.0% (1) | Depression | 4.0% (1) | (0) |
| Grandiosity | 16.0% (4) | 20.0% (1) | Motor retardation | 32.0% (8) | (0) |
| Suspiciousness / Persecution | 16.0% (4) | 60.0% (3) | Uncooperativeness | (0) | (0) |
| Hostility | 12.0% (3) | 40.0% (2) | Unusual Thought Content | (0) | (0) |
| **Negative Symptoms** | | | Disorientation | 12.0% (3) | (0) |
| Blunted affect | 32.0% (8) | (0) | Poor attention | 4.0% (1) | 40.0% (2) |
| Emotional Withdrawal | 4.0% (1) | (0) | Lack of Judgement and Insight | (0) | (0) |
| Poor Rapport | 8.0% (2) | (0) | Disturbance of Volition | (0) | (0) |
| Passive/ Apathetic Social Withdrawal | 12.0% (3) | (0) | Poor Impulse Control | 8.0% (2) | (0) |
| Difficulty in Abstract Thinking | (0) | (0) | Preoccupation | (0) | (0) |
| Lack of Spontaneity and Flow of Conversation | 20.0% (5) | (0) | Active Social Avoidance | (0) | (0) |
| Stereotyped Thinking | 4.0% (1) | 40.0% (2) | | | |
| **Physical Signs** | | | **Other Symptoms** | | |
| Tachycardia | 24.0% (6) | 20.0% (1) | Insomnia | 40.0% (10) | (0) |
| Hypertension | 4.0% (1) | (0) | Suicidal Ideation | 24.0% (6) | 40.0% (2) |
| Hypotension | (0) | 20.0% (1) | Self Harm | 8.0% (2) | 20.0% (1) |
| Diaphoresis | 8.0% (2) | (0) | Amnesia | 12.0% (3) | (0) |
| Mydriasis | 4.0% (1) | (0) | Loss of Consciousness | 12.0% (3) | (0) |

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